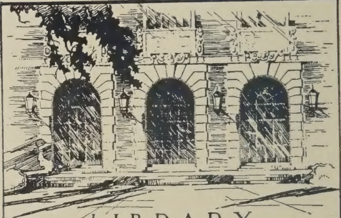
The Acid-Base Balance of the Body

Its Relation to Health and Disease



The Acid-Base Balance of the Body

Its Relation to Health and Disease

Table of Contents

Foreword

It is impossible to give even a brief outline of this wide subject, without devoting some space to a definition of the expression pH.

This entails a short preliminary discussion of the chemistry of body fluids before passing on to the clinical indications for alkali therapy.

We have, therefore, divided the book into two sections. *Part One* deals with purely theoretical considerations; *Part Two* with disturbances in the acid-base balance as they are found in actual practice.

PART ONE

The Acid-Base Balance of the Body

Until recent years little consideration was given to the question of the acidity or alkalinity of body fluids. But of late the importance of maintaining or restoring the acid-base balance in the prevention and treatment of disease has become a major problem of physiological and clinical research.

Progress in this direction has been so rapid that a new field may be said to have opened to the clinician, based on a greater knowledge of the chemistry of the body.

In this connection certain terminology has been inherited by us from our misinformed ancestors and a number of new terms has arisen to meet the newer knowledge. Some confusion has naturally followed, to overcome which it is necessary to become familiar with new words and phrases as well as to understand more thoroughly the action of salts, bases and acids in health and disease.

Terminology

The body consists essentially of proteins, fats, carbohydrates, inorganic salts, carbon dioxide and

water—the latter constituting at least 75% of the total body weight (1). The percentage of any class of constituents in the body is fairly constant at all times.

Electrolytes and Ions

It has been found that many inorganic salts, bases and acids in solution are capable of transmitting an electric current. Such substances are termed "electrolytes."

This ability to carry an electrical current is satisfactorily explained by the Ionic Theory, which hypothesizes that in a solution of electrolytes a process of dissociation takes place, the molecule being broken down into ions, one class of ions carrying a positive charge and other ions carrying a negative charge of electricity. Thus in the case of sodium chloride, for example, there would be present in the solution:

(a) sodium chloride molecules, carrying no charge;
(b) sodium ions, carrying a positive charge;
(c) chloride ions, carrying a negative charge.

Acids and Bases

The behavior of acids, bases and salts in water solutions is due to the activities of their ions. In

this connection, two types of ion are especially involved, namely *hydrogen ion* and *hydroxyl ion.* If the hydrogen ions are in excess of the hydroxyl ions, a solution is acid; if fewer, the solution is alkaline.

Dissociation

Some acids and bases are spoken of as "strong," while others are described as "weak." The essential difference lies in the degree of dissociation into ions. Each substance has a "dissociation constant," which differs with the individual substance. This means that not all substances in solution divide into their respective ions to the same degree.

For example, in an acetic acid solution, there are more of the combined hydrogen acetate molecules than there are of the hydrogen and acetate ions. Hence, acetic acid is a weak acid.

On the other hand, in a hydrochloric acid solution, more of the substance is in the form of hydrogen and chloride ions than in the form of hydrogen chloride particles. This, then, is a strong acid.

What is pH?

Even distilled water breaks up slightly into its respective ions. The number of hydrogen ions here equals 0.0000001 grams per liter. This is expressed

in terms of the power of ten, thus: $[H^+] = 10^{-7}$. Likewise, the hydroxyl ions also equal $\frac{1}{10,000,000}$ gram-molecules per liter, or, $[OH^-] = 10^{-7}$. In other words, the two opposing ions balance, and the solution is neutral.

In view of the large figures involved, and the resultant confusion, Sörenson has introduced the term pH to simplify the nomenclature. By this method, the ten and the minus sign are omitted, leaving only the exponent. Thus, water has a pH of 7.

The total dissociation is always 10^{-14}. Therefore, as the hydrogen ions increase, the hydroxyl ions decrease proportionately. For this reason, we are able to omit consideration of the hydroxyl ions and mention only the hydrogen ion concentration, remembering that the total is always 14. The pH, therefore, is based only on the hydrogen ion concentration.

To summarize, *a pH of greater than 7 is alkaline, or basic, while a pH of less than 7 is acid. The farther away from 7, the more acid or alkaline.*

pH of the Body Fluids

Normally, the pH of the blood is confined within the limits of 7.3 and 7.5. The maximum range

of toleration, however, is between 7.0 and 7.8 (1).

Acidosis and Alkalosis

The body fluids, therefore, are always slightly alkaline. A pH of 7.5 or over is called an "alkalosis" or "hyperalkalinity," while a pH less than 7.3 is variously termed "acidosis," "hyperacidity," or "hypoalkalinity." While the latter term more correctly defines the condition, "acidosis" is more popular in the literature and is most widely used by clinicians. For this reason we shall confine ourselves to the terms "alkalosis" and "acidosis," remembering that at no time does the blood give an acid reaction.

Buffer Salts

The manner in which the body fluids are kept physiologically neutral is of great interest and importance. Briefly, this is accomplished in three ways: by the action of buffers, or tampons (those compounds that resist changes in pH when an acid or alkali is added); by respiration; and by excretion (4). We are particularly interested in the buffer salts of the body, which are comprised of both organic and inorganic substances (3).

The principal organic buffers are the proteins, which, because of their amphoteric properties, combine equally well with acids or bases. The dual

character of this type of buffer is due to the protein molecule, which contains both amino (NH_2) and carboxyl (COOH) groups. The amino group functions as an alkali and combines with acids, whereas the carboxyl group assumes acidic properties and combines with bases.

Graphically, the actions of the various types of inorganic buffer may be shown in the form of chemical equations, as follows:

1. *Bicarbonates*

$$\begin{array}{ccccc}
NaHCO_3 & \rightleftarrows & Na^+ & + & HCO_3^- \text{ (An extremely weak acid)} \\
 & & + & & + \\
HCl & \leftrightharpoons & Cl^- & + & H^+ \\
 & & \downarrow & & \downarrow \\
 & & & & H_2CO_3 \\
 & & NaCl & & \downarrow \\
 & & \text{(Excreted by Kidneys)} & & H_2O + CO_2 \text{ (Excreted by Lungs)}
\end{array}$$

This equation may be summarized as follows:

$$NaHCO_3 + HA \text{ (Any Acid)} \rightarrow CO_2 + H_2O + \underset{\text{(A Sodium Salt)}}{NaA}$$

2. *Carbonic Acid (Carbon Dioxide)*

$$\begin{array}{ccccccccc}
CO_2 + H_2O & \leftrightharpoons & H_2CO_3 & \leftrightharpoons & H^+ & + & HCO_3^- \\
 & & & & + & & + \\
 & & NaOH & \leftrightharpoons & OH^- & + & Na^+ \\
 & & & & \downarrow & & \downarrow \\
 & & & & H_2O & & NaHCO_3
\end{array}$$

This equation may be summarized as follows:

$$\underset{\text{(An Alkali)}}{NaOH} + \underset{\text{(Carbonic Acid)}}{H_2CO_3} \rightarrow H_2O + \underset{\left(\substack{\text{A much weaker} \\ \text{Alkali than NaOH}}\right)}{NaHCO_3}$$

3. *Phosphates*

In the presence of strong acids di-sodium phosphate combines with them to produce a weaker acid. By contrast in the presence of strong bases the blood supplies acid sodium phosphate to act as a buffer and produce by combination a weaker base.

Respiration

The chief waste product of oxidation is carbon dioxide. This is carried as carbonic acid in the blood stream until it finally reaches the lungs and is released. The concentration of carbonic acid in the blood regulates the depth of breathing by stimulation of the respiratory center in the brain. Thus with increased acidity the breathing becomes faster and more carbon dioxide is released (hyperventilation) which in turn reduces the acidity to normal. An alkaline condition, on the other hand, results in diminished aeration and allows the acid (CO_2) to accumulate in the body.

Excretion

When the buffer salts and respiratory system are overtaxed by acid, the body rids itself of acid excess by way of the kidneys, the sudoriferous (sweat) glands, and the alimentary canal, the kidneys being the most important agent for this purpose.

The urine may become as acid as pH 5.0 or as alkaline as pH 8.0. This is due to the ability of the kidney to combine acids with the least amount of base in the presence of acidosis, and by contrast, to utilize the greatest combining power of acids in the presence of an alkalosis. The sweat glands act similarly to the kidneys.

In the case of the alimentary canal Nature makes use of the urge to vomit in pathological cases as a means of keeping the digestive fluids normal in reaction. Also the normal fecal matter is found to contain certain electrolytes, indicating the function of the bowel in controlling the acidity of the body.

The Carbonic Acid-Bicarbonate Ratio

Carbon dioxide may exist in the blood in four forms: free CO_2, carbonic acid (H_2CO_3), bicarbonate ($BHCO_3$), and carbonate (B_2CO_3), although actually only bicarbonate and carbonic acid occur in appreciable quantities (8). The two latter constitute the most important buffers of the body and upon their interrelationship depends to a great extent the acidity of the body.

When the ratio $\frac{NaHCO_3}{H_2CO_3} = \frac{20}{1}$, the pH of the

body may be said to be 7.4 (Hartmann), other factors being unchanged. This ratio is considered normal. It would seem that such a fraction would tend toward alkalinity, but it must be remembered that blood serum is normally slightly alkaline and that weak acids require a large amount of alkali to alter their reaction to any given extent; carbon dioxide, for example, requires 24 times as much alkali as acetic acid to bring about a definite alteration (Stewart).

This peculiarity enables the body to possess a greater potential alkalinity than the titratable alkalinity. The bicarbonate is held in reserve by carbonic acid, but when alkali is needed, the carbonic acid is excreted in the form of CO_2 and the alkali released for utilization.

Part Two

Disturbances of the Acid-Base Balance of the Body

Henderson (9) has stated: "Acidosis is one of the commonest of pathological states. Indeed, I think that it is probably more common than fever. Therefore one may conclude that in serious illness the test for acidosis should always be made, especially because it is often a very simple matter to repair the defect."

Acidosis is defined as any condition in which the carbonic acid-bicarbonate ratio of 1:20 is increased so that the resulting fraction is greater than 1/20. (10). When the buffers of the body are capable of neutralizing the excess of acid so that no change in acidity is produced, the condition is termed a compensated acidosis. If the acid is too great for the buffers present to overcome, uncompensated acidosis is the result. Corresponding changes toward alkalinity may result in a similar manner.

It may be seen from the above that many factors are responsible for an acidotic condition. Faulty digestion, disturbed excretion, dehydration, poor respiration, ingestion of acids or alkalis, circulatory disturbances, infections and many other causes may

contribute to the production of an acidosis or an alkalosis.

A summary of some of the commoner conditions in which an acidosis represents part of the clinical picture is appended.

Kidney Disorders

An acidotic condition is almost always found present in the common types of nephritis, especially in the later stages (11). Normally, urine is slightly acid, having a pH of about 6.0. (12). This is an indication that the kidney helps to excrete acids produced by metabolism. In renal insufficiency acidosis results from continued acid intoxication (13). Acids such as phosphoric and sulphuric are insufficiently removed and there is an abnormal retention (14).

Fisher, Henderson and others have drawn attention to the important role of alkali medication in the treatment of various types of nephritis. Henderson, however, objects to the rather large dosages of bicarbonate recommended by Fisher in these conditions, feeling that the excessive use of the single salt may constitute a grave source of danger.

Children's Diarrheas

Arrington (15) states that severe, watery diarrhea tends to produce changes in the direction of

acidosis, because of (1) extensive loss of body water, anhydremia, dehydration; (2) loss of body salts; (3) starvation.

The treatment of the above would be (1) replacement of body fluids by water so as to restore the blood volume and flow; (2) production of diuresis so that accumulated anions such as phosphate, sulphate and chloride may be excreted in combination with ammonia and thus release the base for restoration of bicarbonate; (3) more rapid restoration of bicarbonate in severe cases by the administration of that salt as such; (4) whereever possible, direct removal of the cause of the diarrhea.

Powers (16), Howland and Marriott (17), and others have directed attention to the importance of recognizing this clinical entity and basing active treatment on the correction of the acidosis.

Other Causes of Acidosis in Children

Leenhardt and Chaptal (18) note that children develop acidoses identical with those encountered in adults. They report observations of renal, circulatory and diabetic acidosis in young patients.

Acidosis was found as a complication in several cases of rickets, acute gastro-enteritis, abiotrophy and leukemia.

Crawford (19) describes a frequent type of condition encountered in children, characterized by a sudden onset of high fever, tympanitic abdomen with areas of dullness, air hunger, dry nose and throat and an acetone breath. Thus he subscribes to the theory that an acidosis may result from absorption of colonic poisons from the small intestine.

Fitch (13) and Umana (20) note that the common clinical picture of infantile acidosis is frequently observed in children suffering from rickets and presenting symptoms of convulsions accompanied by severe crises. In older children the attacks present the picture of cyclical vomiting, recurrent bilious attacks such as headaches, etc. Fitch believes overfeeding to be a common cause of an acidotic condition in children.

Chapin and Pease (21) studied 34 cases of acidosis in babies. They believe that the acidosis symptoms in these cases may result from the split products of proteins. Alkaline treatment helped to correct cases of cyclic vomiting which had apparently resulted from acidosis.

Circulatory and Respiratory Conditions

Gorsky (5) refers to the retention of carbon dioxide in conditions of defective blood circulation

where there is not sufficient aeration of the blood and consequent removal of CO_2. He refers specifically to cardiac disease with failure of compensation and to lung diseases such as emphysema and lobar pneumonia. In these cases there is no trace of acetone or diacetic acid in the urine and the only positive finding from urinary examination is an increased ammonia output.

Palmer (23) finds that patients suffering from acute lobar pneumonia excrete a large amount of organic acid. Metabolism is so affected during the febrile stage of pneumonia that considerable amounts of acid substances are produced.

Ely (24), Goldstein (25) and others have reported on the apparent value of alkalis as part of the treatment of pneumonia and influenza.

During the last influenza epidemic Ely treated 26 critical cases of pneumonia, 100 cases of lobular pneumonia (5 in pregnant women), in all of which he prescribed early elimination, persistent saturation with alkaline bases. There were few fatalities in the cases so treated. The chief cause of death during the epidemic is ascribed by him to acidosis and hence the great importance of instituting thorough alkalinization.

The Common Cold

Whether a state of acidosis constitutes a pre-

disposing cause or a result of a cold is still a matter of debate. But it appears to be well established that an acidotic condition is usually found present and therefore that the administration of alkalis should constitute an essential branch of treatment. Many authorities have suggested that the administration of alkalis in the very early stages of a cold may prove abortive by aiding in building up the patient's resistance.

In searching for a frequent cause of colds, Weaver (26) finds that many diseases of the respiratory tract appear to follow attacks of indigestion brought on by over-eating of over-rich foods and consequently toxic absorption from the bowel. He contends that the resulting toxic condition of the blood stream hinders the nourishment of the mucous membrane of the respiratory tract, the bacteria multiplying in consequence in the weakened membrane and resulting in colds, sinusitis, pharyngitis and tonsillitis.

Fantus (27) classifies the common cold, influenza and grippe under the old term "catarrhal fevers." He emphasizes the importance of attempting to restore the lost immunity with alkalis, stressing that there is a clinical tradition that alkaline medication favors recovery and prevents complications.

Pregnancy

Stieglitz (28) considers that a mild acidosis occurs in normal pregnancy, particularly during the last weeks. Hasselbalch and Gammeltoft (29), Losee and Van Slyke (30) and many other investigators have reached this conclusion. Fischer (31) contends that the presence of an acidosis helps to aggravate the nephritides occurring in pregnancy. He argues that acidosis during this period may result from starvation consequent upon vomiting, nausea and the absurd dietary restrictions frequently laid down for this type of patient.

McComb (32) refers to the frequence of pyelitis during pregnancy in which large doses of alkalis with urinary antiseptics are indicated. In colon infections with acid urine, alkalis should be pushed until the urine is strongly alkaline.

Pre- and Post-Operative Acidosis

McCrossin (33) states that since Crile first used the Van Slyke method of determining the diminution in the alkali reserve, post-operatively, special attention has been paid to the influence and prophylaxis of anesthesia acidosis.

Crile as early as 1914 though advocating the use of morphia pre- and post-operatively states specifically that in cases of impending acidosis its use

is contra-indicated, since it interferes with or prevents the neutralization of the acidity in the blood. In its place he recommends bromides per rectum (chloral and bromide).

Morriss (34) discusses the subject of prophylaxis against anesthesia acidosis very thoroughly. His conclusions are: (1) One influence of the anesthetic is towards the depletion of the alkali reserve. (2) During the first half hour the factor of safety is notably modified and the drop is more profound in the case of chloroform than ether. (3) The initial drop in the alkali reserve is followed by a rebound; from that level there is a gradual decrease until the conclusion of the anesthesia. (4) Preliminary administration of sodium bicarbonate increases the alkali reserve, though the most noteworthy effect of this treatment is to lead to higher values for this factor of safety at the conclusion of the anesthetic. (5) The administration of sodium bicarbonate before operation is a rational precautionary measure against post-operative vomiting.

Russ (35), Fischer (31) and others after careful observation of numerous patients reach the conclusion that those suffering from a pre-operative acidosis constitute poor surgical risks. Often the disease for which they are being treated is

responsible for this condition, but in addition the pre-operative starvation regimen may be mainly responsible. Fischer says that "Unless there are specific reasons against it, a surgical patient should be fed within about six hours of his operation" with special attention to adequate carbohydrate consumption. "In addition, the patient should be fed alkali in some agreeable form."

Crile (37) finds that the hydrogen ion concentration of the blood is increased after the inhalation of anesthetics.

NOTE: Recent literature also refers to a condition of post-operative alkalosis, which is likely to result from operations on the upper part of the intestinal tract. In such cases there is a history of loss of Hydrochloric Acid by vomiting or fistula, dehydration, prostration, low blood pressure, tetany. Treatment calls for 3 things—(1) water, (2) salt, and (3) glucose.

Dermatoses

Dinkin (38) refers to more than 20 cases of chronic urticaria in which favorable results were obtained from the oral administration of sodium bicarbonate. Occasionally relapses occur particularly at the time of menstruation or during acute exacerbation of a frequently simultaneously existing cholecystitis. However, by continuing me-

dication with sodium bicarbonate or by resuming it again, the relapses could be counteracted and a complete cure effected. The author advises against intravenous administration of alkali because he considers it unnecessary and even dangerous.

In other itching disturbances such as eczema, serum exanthem, sodium bicarbonate was not effective.

Barber and Semon (39) studied several hundred cases of seborrheic eczema, and though finding that external irritants are usually the exciting causes, there is an underlying metabolic dysfunction in the average patient. In most of these cases the urine was found to be hyperacid and in consequence alkaline treatment was administered by mouth with excellent results. Their alkaline formula consisted of one dram of sodium bicarbonate, 30 grains of potassium citrate, 5 grains of calcium lactate, five grains of magnesium carbonate, and one ounce of chloroform water. This was given thrice daily, one-half hour before meals.

Bianchi (40) after a short survey of 301 cases of burns, gives an account of a series of experiments on rabbits on which he studied the variations in the acid-base equilibrium resulting from

grave burns. He found in every instance a state of acidosis characterized by rapid diminution of the alkali reserve, and a rapid increase in urinary alkalinity. Such manifestations are due to a dysfunction of the renal epithelium which becomes less permeable to acids. In any event, he considers that the acidosis itself may be at least an important associated cause of death and as such should be combated by suitable treatment.

Gastric Hypersecretion

So much has been written on the importance of alkali therapy in the treatment of gastric hyperacidity, gastritis and gastric ulcer that it is hardly necessary to cite authoritative references.

The classical forms of treatment and prophylaxis in these conditions include the frequent administration of alkalis in association with corrective diet and other measures.

In the milder types of stomach hyperacidity with the usual symptoms of sour stomach, pain coming on some time after eating, etc., the relief afforded by alkali medication is an established fact in therapeutics.

Asthma

Cameron (41), Oriel (42), Adam (43) and

others, have offered evidence to show the presence of acidosis in a large percentage of asthmatic cases.

Cameron in an extensive clinical investigation found the alkali reserve lowered in every case, and regards the treatment of the underlying acidosis as an important phase of therapy.

Investigation has shown that there is usually an increase of total acid in the urine, with an increase of ammonia-combined acid. The latter often persists for some time after the spasm has ceased.

After thirty years' clinical experience in over 1300 cases, Adam has found it expedient to forbid acid-forming foods to asthmatics.

In association with diet regulation the importance of alkali administration is stressed where definite evidence of an acidosis is found.

Association of Alkalis with Salicylates

Johnson (44) found that the readily absorbable salicylates, particularly the sodium and ammonium salts as well as acetylsalicylic acid when administered orally and hypodermically caused a definite and generally marked respiratory stimulation with depletion of the alkali reserve of the blood in rabbits and cats. On the basis of experi-

mental work it was concluded that the use of bicarbonate together with salicylates in rheumatic fever and also in the treatment of salicyl poisoning is rational.

Osler (45), Hanzlik (46) and others have emphasized the importance of associated alkaline treatment because it helps to neutralize the acid toxins of the bacteria of rheumatism and at the same time tends to lessen the pernicious cardiac dilation which is so often present.

Symptoms and Diagnosis of Acidosis

Discussing the early symptoms of acidosis, Fitch (13) enumerates the following: Unusual fatigue, lack of appetite, breathlessness, gastrointestinal acidity, nausea, vomiting, headache, aching in the muscles, sleepiness, flushed face and a sweet, fruity odor of the breath.

Gorsky (5) describes the symptomatology as a complex of hyperpnea without cyanosis, nausea, vomiting, headache, vertigo, faintness and debility. In severe cases there is stupor or coma. Fever is frequently present and the condition may present such toxicity that typhoid fever is simulated and often suspected. Often there is considerable abdominal tenderness even suggesting appendicitis.

Referring to the various methods for diagnosing the presence of acidosis the same author lists

(1) determination of the pH condition of the blood; (2) determination of alkali reserve of the blood; (3) determination of carbonic acid tension of the alveolar air; (4) determination of the nitrogen in the form of ammonia in the urine; (5) presence of acetone and diacetic acid in the urine.

The determination of the pH condition of the blood is usually not done because this test is indicated only when the acidosis is not compensated and the pH is already diminished. The important thing is to diagnose acidosis before the pH is changed. On the other hand we cannot diagnose acidosis unless we know the clinical history of the patient, because the laboratory findings are not the same in all cases of acidosis.

From the standpoint of the general practitioner, simpler diagnostic methods have been suggested. For example, Sellards (47) and Palmer and Henderson (48) suggest a simple method, as follows: They bring out the fact that in normal patients from 5 to 10 grams of sodium bicarbonate are sufficient to change the reaction of the urine to neutral. They therefore suggest that if this does not occur and the urine remains definitely acid in any case under consideration where nephritis can be ruled out, it is almost proof

positive that a condition of acidosis is present.

Another very simple test suggested by Yandell Henderson (49) is based on the length of time that the patient can hold his breath. He states that a normal individual can hold his breath for from 30 to 40 seconds, but this period diminishes proportionally to the reduction in blood alkali. It is interesting in this connection to note that this method is regarded as particularly valuable when testing patients prior to the administration of an anesthetic. The author suggests that general anesthesia is contra-indicated if the patient is unable to hold his breath for at least 20 seconds.

The Clinical Advantages of a Balanced Alkali

Referring to the usual methods of treating hyperacidity and acidosis, it has been stated that the "cure" may sometimes prove worse than the disease. This frequently applies where massive doses of single alkalis are employed. Numerous writers have drawn attention to the danger of setting up an imbalance with the possibility of the production of an alkalosis from this procedure.

The clinical success of BiSoDoL is built around its carefully balanced formula. In actual practice,

BiSoDol appears to give more satisfactory results from lower dosage, with less danger of setting up an alkalosis.

From the patient's standpoint, also, we must not forget that BiSoDoL possesses other advantages. It differs from the ordinary types of alkali prescribed in being unusually pleasant to take. BiSoDoL is a snow-white powder—soft, thoroughly triturated, and free from the slightest objection as to odor or taste.

Dosage.

For digestive disturbances, 1 teaspoonful in water or milk after meals or when required. Quick relief can be promised.

For systemic medication, to aid in replenishing the alkali reserve, BiSoDoL should be administered in smaller but more frequently repeated doses; usually, ½ to 1 teaspoonful every two hours.

Bibliography

1. Bodansky, M., Introduction to Physiological Chemistry. 2nd ed., 1930. John Wiley & Sons.

2. Cutting, R. A., Principles of Pre- and Post-operative Treatment, Am. J. Surgery, 12:345, 1931.

3. Stewart, G. N., A Manual of Physiology. 8th ed. Wm. Wood & Co., 1921.

4. Hartmann, A. F., Col. Med., 26:373, Nov. 1929.

5. Gorsky, S., Med. J. & Rec., June 4, 1930, p. 552.

6. Lewis, R. C., Col. Med., 26:368, Nov. 1929.

7. Kahn, M., Med. Life, 32:189, 1925.

8. McLeod, J. R., Physiology and Biochemistry in Modern Medicine, 5th ed., C. V. Mosby Co., 1927.

9. Henderson, L. J., Acidosis, Science, 1917, v. 46, p. 73.

10. Mathews, A. P., Physiological Chemistry, 5th Ed., Wm. Wood & Co.

11. Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C., J. Clin. Inv. 6:517, 1929.

12. Henderson, V. E., and Scott, J. M., Can. M. A. J., June 1931, p. 833.

13. Fitch, W. E., Med. World, Dec. 1930, p. 455.

14. Marriott, M., and Hartmann, A. F., J. A. M. A., 91:1675, 1928.

15. Arrington, G. L., New Orleans M. & S. J., 83:388, 1930.

16. Powers, G. F., Am. J. Dis. Child., 32:232, 1926.

17. Howland, J. L., and Marriott, M., Quart. J. Med. 11:289, 1918.

18. Leenhardt, E., and Chaptal, J., Rev. Franc. de Ped. 3:745, 1927.

19. Crawford, L. P., N. E. J. of M., Sep. 17, 1931, p. 577.

20. Umana, C. T., Rev. franc. de pediat. 2:717, 1926.

21. Chapin, H. D., and Pease, M. C., J. A. M. A. 67:1353.

22. Labbé, M., and Nepveux, F., Acidose et alcalose. Masson & Cie.

23. Palmer, W. W., Am. J. Clin. Med., Dec. 1918, Jan. 1919.

24. Ely, T. C., J. A. M. A., 71:1431, 1918.

25. Goldstein, H. I., Am. J. Clin. Med., Jan. 1919.

26. Weaver, D., J. Indiana S. M. A., Jan. 1931, p. 8.

27. Fantus, B. J., J. A. M. A., 75:1695, 1920.

28. Stieglitz, E. J., Am. J. Ob. & G. 21:26, 1931.

29. Hasselbalch and Gammeltoft, Biochem. Zeitschr., 68:206, 1915.

30. Losee, J. R., and Van Slyke, D. D., Am. J. Med. Sc., 153:97, 1917.

31. Fischer, M. H., Edema and Nephritis, 2nd ed., 1915.

32. McComb, Can. M. A. J., Sep. 1931, p. 296.

33. McCrossin, W. P., Col. Med., 26:360, 1929.

34. Morriss, W. H., J. A. M. A., 1917.

35. Russ, W. B., J. A. M. A., 61:1618, 1913.

36. Howell, W. H., Textbook of Physiology, 11th Ed., W. B. Saunders Co.

37. Crile, G. W., S. G. & O., 20:680, 1914.

38. Dinkin, L., Med. Klin., 26:1917, 1930.

39. Barber and Semon, B. M. J., 2:245, 1918.

40. Bianchi, G., Arch. Ital. di Chir. 29:275, 1931.

41. Cameron, Med. J. & Record, p. 526, 1929.

42. Oriel, Guy's Hospital Report. p. 486, Oct. 1929.

43. Adam, J., Clin. Med. & Surg. p. 793, Nov. 1931.

44. Johnson, C. C., J. A. M. A., 94:784, 1930.

45. Osler, Sir W., Principles and Practice of Medicine, 10th ed., D. Appleton & Co., 1926.

46. Hanzlik, P. J., Medicine, 5:354, 1926.

47. Sellards, A. W., Bul. Johns. Hopkins Hosp., 25:141, 1914.

48. Palmer, W. W., and Henderson, L. J., Arch. Int. Med. 16:109, 1915.

49. Henderson, Y., J. A. M. A., 63:318, 1914.